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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/804,409	KIEFFER ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,34-36,38,40,43,47,49,51,54,55,71-73,76,78,80,82,85-88 and 114-120* is/are rejected.

7)☒ Claim(s) *13,34-36,38,40,43,47,49,51,54,55,71-73,76,78,80,82,85-88 and 114-120* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Disposition of Claims: Claims pending in the application are 13,34-36,38,40,43,47,49,51,54,55,71-73,76,78,80,82,85-88 and 114-120.

Continuation of Attachment(s) 6). Other: Web Page 1 of 9/6/06 and Web Page 2 of 9/6/06.

DETAILED ACTION

Applicant's amendments and argument of 10/11/05 have been entered.

Claims 37, 48, 52, 79, 83, and 89-113 are cancelled.

Claims 31, 38, 40, 47, 49, 71, 73, 78, 80, and 87-88 are amended.

Claims 114-120 are newly added.

Claims 31, 34-36, 38, 40, 43, 47, 49, 51, 54-55, 71-73, 76, 78, 80, 82, 85-88, and 114-120 are presently pending.

Election/Restrictions

The presently presented claims appear to all embrace the invention originally elected.

Hence, Claims 31, 34-36, 38, 40, 43, 47, 49, 51, 54-55, 71-73, 76, 78, 80, 82, 85-88, and 114-120, are presently considered.

Claim Status, Cancelled Claims

In light of Applicant's cancellation of Claims 37, 48, 52, 79, 83, and 89-113, all rejections and/or objections to such claims are rendered moot, and thus, are withdrawn.

Claim Objections

In light of Applicant's amendments, the objections of Claims 47 and 78, objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, are withdrawn.

Claims 31 and 71 are objected to for claiming the same type of cell twice in a Markush group of stem cells. To wit, in each of these claims the term "pluripotent or multipotent progenitor cells" is present twice. The claims are not rejected for lack of clarity because the Examiner has no reason to believe that Applicant is attempting to claim distinct subject matter twice in each of the limitations.

Claims 34-36, 38, 40, 43, 47, 49, 51, 54-55, 72-73, 76, 78, 80, 82, 85-88, and 114-120 are objected to for depending from an objected to base claim without overcoming the objection to the base claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In light of Applicant's amendments, the rejections of Claims 31, 34-36, 38, 40, 43, 47, 49, 51, 54-55, 71-73, 76, 78, 80, 82, and 85-88 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, are withdrawn.

Claims 31, 34-36, 38, 40, 43, 47, 49, 51, 54-55, 71-73, 76, 78, 80, 82, 85-88, and 114-120 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 31 and 71each now contain limitations to both gut or GI mucosal tissue cells which are stem cells or endocrine cells. These two limitations appear to encompass the same subject matter, and therefore, it is unclear what the are the metes and bounds of such alternating terms. To wit, both the Gut and GI tract encompass the viscera, which comprises the upper, middle, and lower digestive tract. For example, definition of the gastrointestinal tract includes "the GI tract or the alimentary canal or the gut" (HTTP://www.answers.com/topic/gastrointestinal-tract). Similarly, the definition of the gut includes "The alimentary canal or a portion thereof, especially the intestine or stomach" (HTTP://www.answers.com/topic/gut). Therefore, because both definitions include the alimentary canal, which is the whole digestive tract from the mouth to the anus, it is clear that the Artisan would consider these terms to be co-extensive, including the same tissues and cells.

Claims 31 and 71 are rejected for not claiming a complete method. To wit, Applicant's method of treatment is drawn to treatment of diabetes or undesirable body mass/obesity. However, at no point is the treatment effected. Applicant simply claims that "wherein orally contacting ... [results in decrease of insulin or secretion of leptin in an amount effective to treat the appropriate disorder]". However, such wherein clause is not required to be effected in the method. Therefore, the method, drawn to treatment, is not complete.

Claim 35 recites the limitation "the subject has a fasting plasma glucose level greater than 110 mg/dl. It is unclear if such fasting glucose level is prior to, or after treatment, or both.

Claims 43 and 76 each recite the term "promoter expression function". The metes and bounds of such limitation are unclear. To wit, promoters are not expressed, but promote the

transcription of other, adjacent, sequences. Hence, the metes and bounds of such function are not clear.

Claim 54 recites the limitation "the [promoter] in operable linkage with a nucleic acid further comprises a vector". The metes and bounds of such limitation are unclear. To wit, promoter regions in operable linkage are not generally considered to comprise a vector, but vectors are considered to comprise nucleic acids, which comprise promoters and nucleic acids encoding proteins. Hence, it is unclear if Applicant is claiming a composition of a nucleic acid and a vector, or whether Applicant is claiming a vector comprising the nucleic acid. However, for purposes of compact prosecution it is being interpreted to mean to a vector comprising the nucleic acid.

Claims 54 and 85 each recite the limitation "the [promoter] in operable linkage with a nucleic acid further comprises a vector". The metes and bounds of such limitation are unclear. To wit, promoter regions in operable linkage are not generally considered to comprise a vector, but vectors are considered to comprise nucleic acids, which comprise promoters and nucleic acids encoding proteins. Hence, it is unclear if Applicant is claiming a composition of a nucleic acid and a vector, or whether Applicant is claiming a vector comprising the nucleic acid. However, for purposes of compact prosecution it is being interpreted to mean to a vector comprising the nucleic acid.

Claims 71-72 recite "undesirable body mass". The term "undesirable body mass" is vague and indefinite, simply depending on the result of the analysis or opinion of the person determining that such body mass is undesirable. Hence, the metes and bounds of such term are not clear.

Claims 34-36, 38, 40, 43, 47, 49, 51, 54-55, 72-73, 76, 78, 80, 82, 85-88, and 114-120 are rejected for depending from a rejected base claim and not overcoming the lack of clarity in such base claim.

Claim Rejections - 35 USC § 112 – new matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47, 49, 78, and 80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's claims encompass the following subgenera of the broad claimed cell types to be transformed in the method:

(i) mucosal tissue endocrine cells, mucosal tissue stem cells, pluripotent progenitor cells, and multipotent progenitor cells, each present in the small intestine;

(ii) mucosal tissue endocrine cells, mucosal tissue stem cells, pluripotent progenitor cells, and multipotent progenitor cells, each present in the stomach.

Applicant claims that these amendments were made to provide antecedent basis, due to the amendments to the broad claims, however, Applicant has not provided any information as to where such subgenera of cell types, present in the particular tissues, is provided. The Examiner

has reviewed the specification, and finds that the closest support is found in the specification, pages 5-6, however, the specific cell types, in the tissues provided, is still not contemplated, but simply a generic mucosal cell of the stomach or small intestine (a.k.a., duodenum).

Hence, because Applicant has not provided where in the originally-filed Application support is found for these limitations, and further, because the Examiner has failed to find any explicit or implicit support, these claims are rejected for comprising new matter.

Applicant is reminded that it is Applicant's duty to provide the support for newly claimed limitations, and not the Examiner's duty to find such support for Applicant.

Claim Rejections - 35 USC § 112 – new matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31, 34-36, 38, 40, 43, 47, 49, 51, 54-55, 71-73, 76, 78, 80, 82, 85-88, and 114-120 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention comprises the selective transformation of any one of several types of cells. However, the methods of transformation cannot selectively transform any specific cell type. Moreover, Applicant has not demonstrated support for such, but only that the various cell types may be transformed.

Hence, these claims are rejected for comprising new matter. Applicant is reminded that it is Applicant's duty to demonstrate support for the invention claimed, and not the Examiner's burden to provide such support.

Claim Rejections – 35 USC § 112 – written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In light of Applicant's amendments and arguments, the rejections of Claims 31, 34-36, 38, 40, 43, 47-49, 51-52, 54-55, 71-73, 76, 78-80, 82-83, and 85-88, under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, are withdrawn.

Specifically, with regard to the promoter, Applicant has demonstrated that the Chromogranin A promoter was well known at the time of filing such that the Artisan would be aware of the essential regions required of the promoter to function.

With regard to the various sugars, polypeptides, amino acids, and fats, although Applicant's own information appears lacking, further consideration by the Examiner demonstrates that it was known in the art that the Chromogranin A promoter responds to gastrin, which increases due to feeding of any of the various compounds claimed, and further, that such increased expression also increases Chromogranin A levels in the plasma (Hocker, et al. (2004) Ann. NY. Acad. Sci., 1014: 97-109 makes clear that chromogranin expression is enhanced in response to gastrin and moved into secretory vesicles, and such was known at the time of filing, as evidenced by the citations to which Hocker refers on pages 97-98. Also, Dimaline, et al.

(1993) Am. J. Physiol., 264(3 Pt 1): G583-88 (ABSTRACT) demonstrates that the same gastrin causes release of Chromogranin A into the plasma from the same cells).

Claim Rejections - 35 USC § 112 – written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31, 34-36, 38, 40, 43, 47-49, 51-52, 54-55, 71-73, 76, 78-80, 82-83, and 85-88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's claims encompass the stimulation of transcription from the GIP promoter by the use of a generic polypeptide and a generic amino acid.

However, Applicant's specification only provides evidence of a single sugar inducing the transcription of GIP promoter: glucose (e.g., EXAMPLES). Therefore, for the other sugars, and the other types of molecules, Applicant's specification relies upon the art to demonstrate possession of such promoter induction of transcription by these entities.

The Art, on the other hand only recognizes carbohydrates and fats as inducing GIP promoter, as evidenced by Tseng, et al. (1993) Proc. Natl. Acad. Sci., USA, 90: 1992-96, page 1995, last paragraph. Hence, the Artisan would not understand Applicant to have been in possession any generic polypeptide or amino acid stimulation of the GIP promoter.

Claim Rejections - 35 USC § 112 – Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

While the rejections of Claims 31, 34-36, 38-40, 43, 47-49, 51-55 and 87 under 35 U.S.C. 112, first paragraph, because the specification did not reasonably provide enablement for the scope of any animal, any chromogranin A promoter, any polypeptide, amino acid, fat, or lipid, or any vector are withdrawn, the following new scope of enablement is provided, which overlaps various previously held aspects, and provides new scopes of enablement.

Claims 30, 34-36, 38, 40, 43, 47, 49, 51, 54-55, 87, 114, 116, and 118 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

(i) A method to ameliorate the high levels of glucose in the blood of a mammal with diabetes, the method comprising:

transforming the cells comprising K cells of the lumen of the duodenum and/or jejunum with a plasmid or viral vector comprising a nucleotide sequence encoding insulin, operably linked to a GIP promoter, via direct administration to the lumen of the duodenum or jejunum, whereby K cells are transformed,

thereby causing the K cells of the duodenum and/or jejunum to transcribe and secrete insulin in response contact with a sugar, polypeptide, amino acid, or fat, such secretion being into the plasma, causing blood glucose levels to decrease,

and thereby causing an amelioration of increased blood glucose levels in the patient after subsequent administrations of the sugar, polypeptide, amino acid, or fat to the patient via alimentary canal administration;

(ii) A method to ameliorate the high levels of glucose in the blood of a mammal with diabetes, the method comprising:

transforming the cells comprising at least one of ECL cells, G-cells, D-cells, or A-like cells of the lumen of the large and/or small intestine with a plasmid or viral vector comprising a nucleotide sequence encoding insulin, operably linked to a Chromogranin A promoter, via direct administration to the lumen of the large and/or small intestine, whereby least one of ECL cells, G-cells, D-cells, or A-like cells are transformed,

thereby causing the least one of ECL cells, G-cells, D-cells, or A-like cells of the large and/or small intestine to transcribe and secrete insulin in response contact with a sugar, polypeptide, amino acid, or fat, such secretion being into the plasma, causing blood glucose levels to decrease,

and thereby causing an amelioration of increased blood glucose levels in the patient after subsequent administrations of the sugar, polypeptide, amino acid, or fat to the patient via alimentary canal administration,

does not reasonably provide enablement for any treatment of diabetes, the selective transformation of any particular cell type, the absence of secretion upon subsequent exposure to the sugar, fat, polypeptide or amino acid, oral delivery of the nucleic acid, GIP promoters active in tissues other than the K cells, Chromogranin A promoters active in cells other than ECL, G, D, or A-like cells of the intestine, or any nucleic acid delivery, or delivery of the sugar, fat,

polypeptide or amino acid which is not into the alimentary canal upstream of the transformed cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 71-73, 76, 78, 80, 82, 85, 88, 115, 117, 119, and 120 (Claim 71 and all of its dependent claims) remain and/or are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons of record and/or for the reasons provided below. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Below, the enablement rejections are readdressed, with due regard to the new bases of the rejections, followed by an answer to Applicant's arguments.

The Law

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention within its full-claimed scope, and that, therefore, Applicant's claims are not enabled to their full-claimed scope. (It is noted that this is written as a scope of enablement, but that scope provided demonstrates a complete lack of enablement for obesity/undesired body mass.)

The Breadth of the Claims

Applicant's claims are broad in many aspects which the Artisan would not find enabled for their broad scope. Below is an analysis of the breadth of the claims.

Claims 31 and its dependent claims are broad for the following aspects: (i) they encompass the selective transformation of many types of cells, including cells outside the gastrointestinal tract (e.g., pluripotent progenitor cells), the production of protein from two separate tissue-selective promoters in a wide variety of cells, a wide variety of nucleic acids for administration, a wide variety of administrations of nucleic acid (e.g., transformation of the intestine by oral administration), selective activity of the Markush group of nutrients on transcription or secretion of insulin, and transformation of the stomach tissues. Lastly, it is noted that Applicant has claimed "intra-cavity delivery", however, dependent claims to such delivery do not require the cavity to which the vector is delivered to be the cavity that is being

transformed (e.g., Claim 115). Hence, such claim is being interpreted to mean to mean any delivery which ends up delivering the vector the appropriate luminal surface.

Claims 71 and it dependent claims are broad for similar reasons as that of Claim 31 and its dependent claims, as well as reasons of record.

The Nature of the Invention and State of the Prior Art

Applicant's invention is in the nature of gene therapy to treat diabetes or unwanted body mass.

With regard to Applicant's claiming of the specific transformation of various types of cells, it is clear to the Artisan that such cell-type specificity is not possible. To wit, no vector is known which selectively transforms the types of cells claimed, without also transforming any other type of cell claimed.

With regard to secretion of the encoded transgene's polypeptide, the Artisan would only understand secretion to be concurrent with increases in transcription. To wit, it is known that the Chromogranin A promoter is activated by gastrin, which also causes secretion of the secretable proteins into the plasma (Hocker, et al. (2001) Gastroenterology, 121: 43-55, e.g., ABSTRACT; Hocker, et al. (2004) Ann. NY. Acad. Sci., 1014: 97-109, e.g., ABSTRACT). Hence, the secretion is tied to the same cause as the promoter activation. Hence, these two activities are not severable with the Chromogranin A promoter systems. Simiarly, with the GIP promoter system, it is known that such secretion is also concurrent with activation of the GIP promoter (Tseng, et al. (1993) Proc. Natl. Acad. Sci., USA., 90: 1992-96, e.g., ABSTRACT; Cheung, et al. (2000) Science, 290 : 1959-62, e.g., ABSTRACT). Hence, similar the Chromogranin A system, with the GIP promoter, the expressed protein's secretion cannot be severed from that of transcription.

With regard to treatment, the term is broad and encompasses more than the increase of insulin levels in the blood in response to glucose, but the restoration of B-cells, the reversal of auto-immunity, reversal of complications, and the various other aspects involved in the pathology of any particular form diabetes. Hence, the Artisan would reasonably predict treatment, but only amelioration of the high levels of plasms glucose present in the blood of diabetics upon ingestion of food, because such secretion of insulin would be reasonably predicted to cause cells to uptake glucose, lowering plasma glucose.

With regard to treatment with vectors comprising GIP promoters, the K cells of the stomach, duodenum, jejunum, and ileum, were the only cells known to have active GIP transcription prior to Applicant's disclosure (e.g., Cheung, et al. (2000) Science, 290 : 1959-62, e.g., p. 1959, col. 2 ; Tseng, et al. (1993) Proc. Natl. Acad. Sci., USA., 90: 1992-96, e.g., p. 1992, col. 1, paragraph 1). Hence, even if other cells are transformed, these cells are the only cells of the body reasonably predicted by the Artisan to make any GIP promoter linked insulin which then may be secreted and effect any level of amelioration.

With regard to treatment with vectors comprising Chromogranin A promoters, the Artisan would only reasonably predict from Applicant's administration to the GI tract that the ECL cells, G, D, and A-like cells are the only cells which could transcribe the operably linked protein, much less secrete it, as these are the only cells of the GI tract which actively transcribe from the Chromogranin A promoter (Hocker, et al. (2001) Gastroenterology, 121: 43-55, e.g., p. 43). Hence, the Artisan would not reasonably predict that any portion of the GI tract or any cell of the types listed in the GI tract could be used to effect such treatment, as only the above-listed cells were known to actively transcribe from the Chromogranin A promoter.

With regard to the types of cells which must be transformed, these cells must be commensurate with those that express from the appropriate promoter, otherwise the treatment wont work as the insulin would not be produced.

With regard to treatment of cells of the stomach and treatment of tissues downstream the stomach in the alimentary canal by administration through the alimentary canal, it is well-known that the stomach has particularly low pH and digestive activities, such that the Artisan would not reasonably predict that any particular nucleic acid vector would transform the cells of the stomach. To wit, adenoviral vectors, which have an extremely wide tropism, do not transform cells of the GI tract by stomach tube (Zhao, et al. (2003) Vaccine, 21: 4022-35, e.g., ABSTRACT). Hence, the Artisan would not reasonably predict transformation of any cells in the stomach or administration by oral administration of the vector, but only cells of the intestine wherein such vectors were not administered through the stomach, but instead, administered directly into the intestinal lumen.

With regard to administrations which provide the vector to the intralumenal surface required, the previous arguments are further modified by the arguments previously of record, in that the Artisan, even if they could predict treatment by the effect of the transformed cells, if the system worked perfectly, the Artisan still could not reasonably predict that any administration would reasonably transform enough cells, to produce enough mRNA and protein therefrom, for a long enough time to have the required effect(s) (e.g., Official Action of 12/20/05, pp. 16-25).

With regard to the use of any nucleotide, Applicant's claims encompass many viral vectors, including naked RNA vectors. However, it is well known in the art that RNAs are generally highly susceptible to degradation, such that transformation of cells in vivo rarely

occurs. Further, if the DNA vector was not a double-stranded DNA, it is not reasonably predicted that the DNA would reach the nucleus and be transcribed at all. Therefore, the Artisan would only reasonably predict dsDNA vectors or viral vectors to be efficacious in transforming cells.

With regard to treating obesity/unwanted body mass, in addition to the same problems above apply, modified with the necessary use of leptin instead of insulin and obesity/unwanted body mass instead of diabetes (such is necessarily true, as it still has the same hurdles to overcome), the art generally recognizes that the results with treatment with leptin are specious at best, and was not reasonably predicted by the Artisan to be efficacious for any particular obesity/unwanted body mass at the time of filing. To wit, Buettner, et al. (2000) Am. J. Physiol. Endocrinol. Metab., 278: E563-69 report "the ability of leptin administration to reverse metabolic abnormalities in the ob/ob mouse and improve insulin action in normal animals has lead to the proposal that leptin may serve as an effective therapy for human obesity." Buettner goes on to caution that before leptin can effectively be used to treat obesity a number of questions remain to be answered. "First, it is not clear that increasing plasma leptin levels will be sufficient to correct the metabolic abnormalities associated with obesity, principally insulin resistance and perturbed lipid and carbohydrate metabolism. Second leptin therapy involving multiple injections has had mixed results both in animal models of obesity and in human trials, and this suggests that alternative strategies such as sustained increases in plasma leptid should be considered." (p. E556). Moreover, Chiesi, et al. (2005) Trends in Pharmacol. Sci., 22(5): 247-54 provides a recent review of the field, demonstrating that such therapies with leptin are similarly not even now considered to be reasonably predictable. To wit, Chiesi discusses the discovery of

leptin, its nature as a feedback regulator, and mouse models which seemed to indicate that it would treat obesity, followed by a small trial where a patient was treated (p. 247, paragraph bridging columns). However, subsequent clinical trial indicated leptin was much less promising than expected (Id., col. 2, paragraph 2), where, even after extremely high doses, weight loss was variable, and average reductions in weight were small (Id.). The author explains many reasons why such results may be found, including, for example, leptin's activity may be at very low concentrations, and increases have no effect, therapeutic efficacy may have been overestimated, human responses are not the same as the mouse, some humans may be resistant to leptin, either due to leptin receptor signaling or transportation of leptin in the body (p. 247, col. 2, paragraph 3). Moreover, Liu, et al. (2005) Drugs of Today, 41(5) : 345-62 adds another complication: obesity and unwanted body mass are actually unlike other genetic diseases, being under the control of many genetic factors (p. 351, col. 2, paragraph 2). Hence, from this, the Artisan could not reasonably predict that any particular obesity or unwanted body mass could be treated, much less detected before obesity occurs such that treatment could be effected, because it is simply not understood well enough, and further a single gene may not be enough.

Furthermore, unwanted body mass encompasses things totally unrelated to leptin and fat, e.g., too much muscle may be unwanted, tumors may be unwanted, as well as many forms of growth on the body. Hence, this is completely unrelated to Applicant's claimed treatment with leptons, and therefore, the treatment is not reasonably predicted for these.

The Guidance and Direction Provided by Applicant

The background of Applicant's specification broadly discusses the difficulties in the use of protein treatment of disorders in general (pp. 1-2) (which expounds the same difficulties with

delivery as that found for the use of any nutrient in general), the use of gene therapy, and the difficulties surrounded by these methods (pp. 2-3), the need for regulated gene expression in certain gene therapy protocols, including diabetes (p. 3), a review of diabetes and the proposal to use surrogate cells for the production of insulin in diabetes treatment by gene therapy, and further emphasizing the need to control production of insulin in diabetes and in other diseases in humans, which is proposed to be satisfied by the invention (pp. 3-4).

The summary of the invention claims that the invention is based, in part, on the production of transformed gut cells that produce insulin, which are able to secrete insulin at physiological levels and restore normal glucose homeostasis in diabetic animals. From this, Applicant summarizes that cells may be transformed with any transgene which will work in similar manner to be controlled to provide a benefit in any disorder. Further, the mucosal cells respond to any nutrient, and may be anything causes increased expression and/or secretion of the transgene.

The specification broadly discusses expression of transgenes in endocrine cells releases the encoded protein into the bloodstream in a regulated manner (pp. 10-11), delivery of GIP linked to human insulin in transgenic mice demonstrates expression and secretion of insulin in the K cells of such mice (p. 11), methods of generating a mucosal cell producing such protein in a regulated manner by a nutrient, which mucosal cell may be any endocrine or non-endocrine cell or any non-fully-differentiated cell (p. 11), vectors (p. 11), various expression control elements (p. 12), GIP promoters which respond to glucose (p. 13), examples of 12 other promoters and/or enhancers for targeting expression to endocrine cells in the gut, including the only mention of chromogranin A (TABLE 1), discussion of various other expression elements,

and response to nutrient to decrease or increase expression of operably linked sequences (p. 15), discussion of nutrients, which may be anything and have any effect to affect production of the protein (p. 16), functional fragments and variants of promoters (p. 16-17), broad mention of many genes that may have promoters that are regulated by other nutrients (p. 17), bacterial nutrient regulated elements (p. 18), non-nutrient response elements (p. 18), a definition of operable linkage (p. 18), a definition that expression control can be effected at transcription, translation, splicing, message stability, etc. (p. 18), a definition that production encompasses expression or secretion, and that such may similarly be effected by the same as the expression control definition (p. 19), additionally signals or stimuli may similarly increase production, and the even if the promoter is not regulated, secretion may be regulated by the stimuli (p. 19), various definitions (pp. 20-21), various transgenes (pp. 21-22), obesity and leptins (p. 23), more transgenes (pp. 23-24), various cell types which are encompassed (pp. 24-26), various definitions, the use of any cell which is adapted grow in mucosa or other tissue, the use of multiple transgenes, transgenic animals, treatment of various disorders, more definitions, methods of introduction of the transgene, pharmaceutical formulations, administrations, stem cells, and instruments for administration (pp. 26-42).

However, such broad discussion does not provide the specific guidance and direction for the Artisan to overcome the lack of reasonable predictability for the breadth of transforming any particular cell type exclusively, promoters active in any of the cell types and therefore, secretion from any of the cell types, non-requirement of transformation of the cells in which the promoter is active, any form of treatment, secretion or transcriptional increases that are not concurrent, any

nucleic acid, stomach cell transformations, any administration, or any obesity or unwanted body mass.

Existence of Examples

Applicant's specification provides three real examples, and a single prophetic example. Example 1 demonstrates the isolation of K cells from a mixed population of tumor tissue derived from a mouse, by expression of GFP from the GIP promoter, which cells, when transformed with another construct of GIP promoter linked to insulin produced insulin in a glucose-dependent manner *in vitro*. In contrast, other cells similarly transformed with the GIP-insulin construct did not produce significant insulin mRNA.

Example 2 demonstrates that transgenic mice having the GIP-insulin construct in transgenic form express glucose in the duodenum and stomach, in K cells. Example 3 demonstrates these mice to survive STZ-induced diabetes.

Example 4 is a prophetic example of intention to perform *ex vivo* therapy with such K cells.

Three more examples have been provided in the form of declarations of Drs. Kieffer and Cheung, both inventors of the present Application.

The Kieffer declaration demonstrates that GAL-4 promoter linked to leptin, used to transform K cells and placed in alginate, which is then put in a mouse intraperitoneal space, then subcutaneously administered RU486 caused apparent increase in leptin production, and reduced mouse weight, even after removal of the RU486. However, such cells were not transformed *in vivo*, are protected from body by the alginate, are not responsive to a nutrient presently claimed, and were not transformed by intra-cavity delivery, and further were exposed to an artificial

nutrient via subcutaneous implant, and is therefore not responsive to food as would be required by insulin. Further, with regard to leptons, and obesity, the problems art remain that it is not reasonably predictable except for the ob/ob mouse to have treatment in any particular patient of any species.

The Cheung declaration of 6/16/04 demonstrates injection of FIV vectors carrying either chromograninA promoter linked to insulin, or CMV promoter linked to DsRed, and AAV vectors comprising a CMV promoter driving the expression of GFP. The vectors were administered by intraluminal incubation of the duodenum or direct injection into the walls of the duodenum. In the case of insulin production, it was responsive to glucose for 14 days, and the duodenum stained for insulin at day 128. However, these vectors were pseudotyped by VSV-G, and as such their tropisms were decidedly distinct from other vectors, being effective for the K cells, but such does not reasonably predict the transformation of enough cells via any vector by any method of administration, given the lack of reasonable predictability above. Moreover, these vectors were driven by a constitutive promoter with strong expression characteristics, the CMV promoter, and as such even less cells than in the case of the presently claimed promoters need to be transformed, because Applicant's claims encompass any portion of the promoter any portion of the activity of the wild-type promoter. Moreover, the CMV promoter is not responsive to any nutrient, except through the standard indirect methods that Applicant is claiming, but Applicant has not shown any particular nutrient in this case either.

The Cheung declaration of 2/14/05 demonstrates the production of pseudotyped FIV vectors carrying the transgenes of insulin or SEAP, operably linked to the GIP promoter or chromogranin A promoter, respectively. These vectors were used to deliver the genes to cells of

the duodenum by intra-lumenal incubation, in mice. These animals demonstrated production of SEAP or insulin at levels of approximately 15 pM, in blood plasma. Even after 120 days, although some mice had stopped expressing insulin, the others continued to do so, and were the only mice protected from STZ-induced diabetic death when subsequently challenged. However, Cheung's vectors were similarly pseudotyped and hence are not reasonably predictable for any other vector type, by any method of administration for the same reasons as the previous paragraph. Moreover, while Applicant has demonstrated up to 120 days, that some mice expressed insulin, others did not, and given that diabetes may take much longer than four months to develop, it is unpredictable to the Artisan that any animal could be treated prophylactically. To wit, if at 120 days, some animals do not express it, the Artisan could not predict that any animal would express it after a longer time frame, and further, if only some express it, the Artisan could not reasonably predict which patients would express it so that they could be treated.

The latest declaration, included with the most recent response, is the Cheung Declaration of 7/11/06.

In this declaration, Dr. Cheung first demonstrates that the Chromogranin A promoter had been known in several species and dissected to the extent that the Artisan would, with reasonable experimentation, be able to arrive at the various promoters encompassed by the promoter fragments encompassed by the claims (paragraphs 9-10). Next, Dr. Cheung demonstrates that several vectors may be delivered to the lumen of the duodenum of rats, effecting blood insulin levels in response to glucose (paragraphs 11-12), and that other types of cells can produce insulin

(paragraphs 13-14). Finally, Dr. Cheung demonstrates that leptin treatment of a specific form of animal obesity, delivered by a specific method, ameliorates that obesity (paragraphs 15-16).

Further, while Applicant has demonstrated some responsiveness to glucose, it is clear from all these examples that glucose responsiveness it not equivalent to treatment and replacing that of a normal islet of langerhans in level and responsiveness. Such is logical because the beta-cells respond not only to glucose but to many other variables of the endocrine system, and as such a single response to glucose is not reasonably predicted to reflect the normal complicated response. However, such is enough to demonstrate amelioration in mammals, as the mouse model of STZ treatment is recognized to obliterate the cells. On the other hand, as mentioned above, in autoimmune diabetes, these same cells may actually be targeted for producing insulin, and as such, prophylactic treatment is again curtailed.

However, the Examples provided by Applicant also question those cell types which can express insulin from the GIP promoter. To wit, Applicant's Example II demonstrates that no expression was obtained in the ileum, when driven by the GIP promoter. Hence, given Applicant's teachings over the prior art, the Artisan would not reasonably predict that any cell of the ileum would be able to express the insulin to effect amelioration.

Moreover, none of these examples, and the previous direction and guidance, demonstrate that any level of treatment could be obtained, that any cell type could be specifically transformed, that the specific types of cells in which the promoter functions do not have to transformed, that the promoters work in any of the cell types, that secretion and transcription can be effected separately, any nucleic acid could be used, that stomach tissue could be transformed, that any form of administration would transform enough cells, produce enough mRNA and

protein therefore to effect treatment, or that any obesity or unwanted body mass could be treated..

Moreover, while Applicant has demonstrated some treatment in ob/ob mice through administration of GTC-1 cells comprising an RU486-Gal4 linked to leptin gene switch, administered to the mouse intraperitoneally, in an alginate gel, the Artisan would recognize this not to translate into treatment of obesity or unwanted body mass in any animal through the gene therapy protocols presently claimed, given the knowledge in the art.

Lastly, the results fail to overcome the various unpredictabilities in the field, as discussed above, and as such the Artisan would have to experiment to find, with reasonable predictability, the majority of the working embodiments.

The Amount of Experimentation Required

For the reasons discussed above, the Artisan would have to experiment to find, *inter alia*, the cell types in which the promoter works, the methods of administration of the vector, the vector/nucleic acid types, the duration of efficacious expression, the amount of efficacy (i.e., whether for any particular disorder, the gene would suffice to express with the nutrient sufficiently to produce any particular level of therapy), and to determine whether, for obesity/unwanted body mass, any particular patient would be treatable at all.

Hence, such experimentation is undue, amounting to inventing Applicant's claimed invention for the Applicant.

Conclusion

Because such undue experimentation is found, Applicant's claims are found, alternatively to have a scope of enablement as given above, or to not be enabled at all.

Response to Arguments – Enablement

Applicant's arguments filed on 7/11/06 have been fully considered but are not found persuasive.

Applicant provides a review of the evidence provided in the specification and prosecution history, and broadly aver that it provides adequate enablement (pp. 14-15).

Such is not persuasive. Applicant fails to demonstrate how the evidence overcomes the analysis of all the evidence of record, including the evidence and reasoning provided by the Examiner. Broad aversion does not take the place of scientific reasoning and/or evidence demonstrating the analysis of the examiner incorrect.

Applicant argues that the newly submitted evidence demonstrates that the cells may be transformed with viral or non-viral vectors without undue experimentation (pp. 15-17).

Such is persuasive, but not for the scope of any nucleic acid (which is somewhat nebulous as to what is not a vector, but for purposes of examination, the Examiner considers any nucleic acid which has the promoter sequence and operably linked protein encoding sequence is a vector, because it can be put into the cell, to make the protein, directly from RNA or indirectly from DNA.

Applicant argues that transformed cells can provide for long term expression of the proteins, the proteins produce levels which appear to be physiologically relevant, and can be produced in response to glucose and other nutrients (p. 16).

Such is partly persuasive. The scope of treatment, however includes full treatment, which is far beyond Applicant's claims. Lastly, the Examiner stands on the reasons of record to

state that any particular unwanted body mass or obesity could not be reasonably predicted to be treatable by the methods claimed.

Applicant argues that other cells than K cells produce insulin (p. 17).

Such is persuasive. They certainly have the ability to do so, but the promoters are not so-able to transcribe in all of the various cell types claimed.

Applicant argues that other nutrients besides glucose could be used (pp. 17-18).

Such is persuasive. That part of the rejection has been withdrawn.

Applicant argues that the recent treatment of rats containing of mutant leptin receptor that results in obesity, by gene therapy with the CMV promoter driving expression of leptin, by intravenous administration, demonstrates the ability to treat obesity and unwanted body mass (pp. 18-20).

Such is not persuasive. The Examiner stands on the reasons of record. At the time of Applicant's invention it was not reasonably predictable, even in rat models wherein leptin is mutated (See previous arguments, and those reiterated above). Moreover, Applicant does not claim such intravenous administration, the transformation of the cells which were transformed in the paper argued above, and the rat leptin model, but instead any animal, with any form of obesity and unwanted body mass. Further, unwanted body masses, such as tumor masses, have no relation here, and hence, could not be treated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 31, 34, 35, 38, 40, 43, 47, 49, 51, 54-55, 87, 114, 116, and 118 rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,503,887 to During and further in view of either Cheung, et al. (2000) Science, 290 : 1959-62 or Hocker, et al. (2001) Gastroenterology, 121: 43-55.

With regard to Claims 31, 34, 38, 40, 43, and 51, During teaches treating patients for IDDM (e.g., col. 1, paragraph 3), by the administration of nucleic acids encoding insulin (e.g., ABSTRACT), which coding sequences are operably linked to tissue-specific promoters (e.g., col. 2, paragraph 5) and may be responsive to glucose (e.g., col. 8, paragraph 3). Such cells include K-cells and L-cells (e.g., col. 7, paragraph 1). Lastly, Claim 1 teaches that any cell of the gut tissue which is an endocrine cell may be used.

With regard to Claims 87 and 114, During teaches the use of various methods of administration, including oral and feed tube feed tube in administration of vector (e.g., cols. 11-12, paragraph bridging).

With regard to vectors, it is noted that During teaches any viral vector (e.g., col. 8, last paragraph and Claim 1), and AAV vectors, which are integrating vectors (e.g., col. 9).

However, During does not teach or suggest either the Chromogranin A promoter, or the GIP promoter, fasting glucose above 110mg/dL, or sugars increasing secretion of insulin.

On the other hand, Cheung, et al. (2000) Science, 290 : 1959-62, e.g., p. 1959, col. 2, describes the GIP promoter for expression in, *inter alia*, K cells (not including claims 54-55). With regard to the use of the chromogranin A promoter, Hocker, et al. (2001) Gastroenterology,

121: 43-55, e.g., p. 43, teaches the Chromogranin A promoter as a glucose responsive that is activated by glucose, and increases secretion in response to glucose.

With regard to glucose levels, Applicant's own specification teaches that normal levels of glucose levels in plasma are 110 mg/dL, and therefore, it is inherent that the subject with diabetes would have a higher level than 110 mg/dL.

With regard to response to nutrients, such is not part of the method, and inherent in the treatment, as patients need food to survive, and as such, they would activate the promoter.

With regard to the various other cell types, those cell types would be inherently treated by the methods of During, because the intestine is generally transformed, and not simply the various cell types. Hence, absent reason to believe otherwise, these other cells are also transformed.

Hence, at the time of invention by Applicant it would have been obvious to modify the treatments of During with the chromogranin A of Hocker or GIP promoter of Cheung. The Artisan would have been motivated to do so in order to treat diabetes, as taught by During. Moreover, the Artisan would have a reasonable expectation of success, as During had taught the method, and Cheung and Hocker had taught the tissue specific promoters.

Note to Applicant

The Examiner is aware that Applicant is attempting to claim the transformation of stem cells which give rise to those cells which produce and secrete the insulin/leptin, and the Examiner agrees that Applicant must have transformed those cells to get the long-term responsiveness to sugars in the examples, however, Applicant is recommended to find another way of claiming such, because it is the specific cell types which are capable of expressing and

secreting into the blood plasma which are required to be transformed to effect the therapy. Moreover, Applicant should take care not to introduce new matter, as Applicant has not specifically identified these cells in their application, but simply avers to those cells that give rise to the cells required, without specifically identifying which cells they are that so give rise to the cell types required.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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